Letter to the Editor

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Letter to the Editor: Optimism for Nontarget Analysis in Environmental Chemistry

We were pleased to read the recent Viewpoint by Hites and Jobst, "Is Nontargeted Screening Reproducible?". This viewpoint initiates an informal scientific dialogue around an important technical research trend that may challenge peer-reviewers and readers alike. The authors' stated purpose was to "stimulate discussion" on questionable aspects of method performance and quality assurance in high-resolution mass spectrometry (HRMS) nontarget analysis (NTA). They also pointed out ambiguities in NTA terminology increasingly being used in publications. While acknowledging that limitations exist with current NTA approaches leaving much room for improvement, here we aim to constructively explore some of the Viewpoint's discussion points. We present an optimistic alternative viewpoint that current NTA instruments and data workflows are already[1] accelerating the rate of contaminant discoveries, are increasing understanding of chemical fate, and already answer important "so what" questions, such as time trends, bioaccumulation potential, and global distribution.[1]

THE ROLE OF NTA IN ENVIRONMENTAL SCIENCES

Environmental chemists have a long tradition of hypothesis-driven discovery of new contaminants based on the development of highly sensitive and quantitative mass spectrometry methods. These traditional targeted approaches continue to have wide application to identify specific new chemicals. However, there is a need for complementary, less targeted, discovery tools in a society where hundreds of thousands of synthetic organic chemicals are in current-use. Brominated flame retardants and perfluoroalkyl substances were discovered using targeted methods, but not until after decades of exposure and widespread contamination. NTA is a response to this challenge by aiming to increase the rate and response-time of contaminant discovery while making discovery increasingly comprehensive. Today's HRMS instruments enable a new and fundamentally more powerful approach thanks to high frequency full scanning (e.g., < 1 Hz) at resolving powers in the range of 10 000−500 000 m/Δm. These advances in analytical tools have been furthered by software development and the application of complementary fields such as cheminformatics, thereby increasing our understanding of contaminants in our environment.

TERMINOLOGY

Terminology around the application and development of NTA can be unclear at best and baffling at worst, and is often used inconsistently across the environmental sciences. Here, we categorize NTA (all work flows except for suspect screening) into two broad categories: *structural elucidation of unknown features* where a feature is defined as a data tuple consisting of three aspects of the analytical instrument output (a chromatographic peak, and m/z of adducts and isotopes) and *class identification* (Figure 1). Structural elucidation is an unbiased approach that aims to discover any unexpected contaminants in a sample based on a prioritization criterion. Class identification focuses on finding chemicals and/or chemical species (i.e., features identified with distinct chemical formulas) with related chemical formulas or structural elements (e.g., naphthenic acids in complex oilfield wastewater) rather than single contaminants. Structural elucidation, depending on the application, may result in features, profiles (i.e., a range of related features in a sample) and/or validation of signatures (i.e., profiles with an accepted forensic value, for example, the use of polycyclic aromatic hydrocarbon ratios for the contamination source identification). For all environmental chemistry applications, harmonization of the employed terminology would be a helpful step forward.

REPRODUCIBILITY

Differences between laboratories in sample preparation, instrumentation or the various software, and databases used for feature structural elucidation and chemometrics can lead to questions regarding the reproducibility of NTA. Nevertheless, diversity in sample preparation and analytical approaches can also lead to more discoveries. Thus, common methods should not be the goal per se. Within-lab method reproducibility can be directly tested and reported in any given study and should reasonably be expected by reviewers. To avoid false positives there are already established confidence levels for reporting the structure of features in NTA[2] and careful attention must be paid to field and laboratory blanks, just as with targeted analysis. Over time, exploratory discoveries made using NTA can be confirmed using targeted methods and absolute concentrations can be quantified. Ultimately, the goal should be to combine targeted and NTA approaches into a single analysis. This melding of complementary analytical tools is the current trend in metabolomics research.

SUCCESS STORIES

During the past decade we have seen considerable advancements in NTA that now enable tentative identification of current-use chemicals without the immediate need for authentic chemical standards. This is largely thanks to an open and multidisciplinary community of chemists, software developers, and cheminformaticians. Recent advances, for example, in signal processing and computing have enabled the rapid screening of a large number of suspected analytes (e.g., Norman SusDat) in multiple samples,[3] and machine learning enables prediction of MS/MS fragmentation patterns based only on the simplified molecular-input line-entry system (SMILES).[4] Moreover, publicly available lists of environmentally relevant chemicals are expanding (e.g., USEPA Comptox Chemistry Dashboard), and suspect lists (e.g.,

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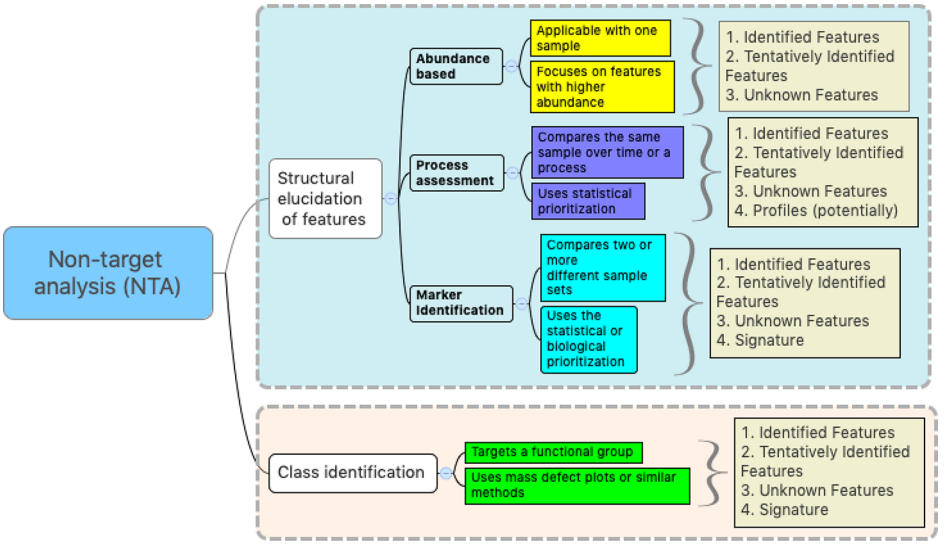

Figure 1. Areas of study for nontarget analysis, the prioritization approaches used, and the NTA outcomes in the environmental sciences.

NormaNEWS through the Norman Network) and HRMS spectral databases are growing to support identification and structural elucidation of unknowns.[5] There are numerous examples of NTA resulting in the discovery of new contaminants and/or their transformation products in complex environmental samples which would not have been possible by traditional methods.[1] We are very much at a point in time where we can start to envision comprehensively characterizing the complex mixture of contaminants in our environment and our bodies. This is a core tenet of the exposome paradigm, to understand the totality of environmental exposures.

LIMITATIONS

NTA is clearly changing the way environmental chemistry, exposure science, and health studies are conducted. There are, however, still limitations to overcome. Frameworks for reporting and publishing data need to be continually developed and adhered to. The accurate structural elucidation of features is, for example, highly dependent on chromatographic and spectral data quality, chemical databases, spectral libraries, and clean blanks. Unequivocal structural identification will always require authentic chemical standards. There are also considerations of transparency and standardization of NTA workflows.

For full transparency, changes in publishing practices are necessary. For example, to allow others to reproduce the results, HRMS raw data files need to be uploaded in open formats to public repositories (e.g., Open Science Framework and/or FigShare). ACS journals certainly have a role to play in developing standardized repositories, as well as requiring sharing of data to be a condition of publication. Already, the NTA community is collaborating to share knowledge and best practices, explore harmonization of methods, and organize interlaboratory trials to directly measure reproducibility between laboratories.[2] NTA is still a new tool but it is maturing rapidly to find routine application in environmental analysis. Through working as a community with open-access resources, transparent sharing of data, and continuing to develop frameworks for reporting and publishing, we believe the true power of NTA will soon be widely realized.

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Notes

The authors declare no competing financial interest.

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